RETROSPECTIVE STUDY WITH FOLLOW – UP OF CHILDREN WITH HEPATOBLASTOMA

A DISSERTATION SUBMITTED TO THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI, IN PARTIAL FULLFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF M. Ch. (BRANCH V) PAEDIATRIC SURGERY

August 2014

CERTIFICATE

This is to certify that the dissertation entitled “Retrospective study with follow-up of children with hepatoblastoma” is a bonafide work done by Dr. Soumitra Saha, Department of Paediatric surgery, Christian Medical College, Vellore, Tamil Nadu, India in partial fulfillment of the University rules and regulations for the award of M.Ch. Paediatric Surgery Degree course under my guidance and supervision during the academic year 2014.

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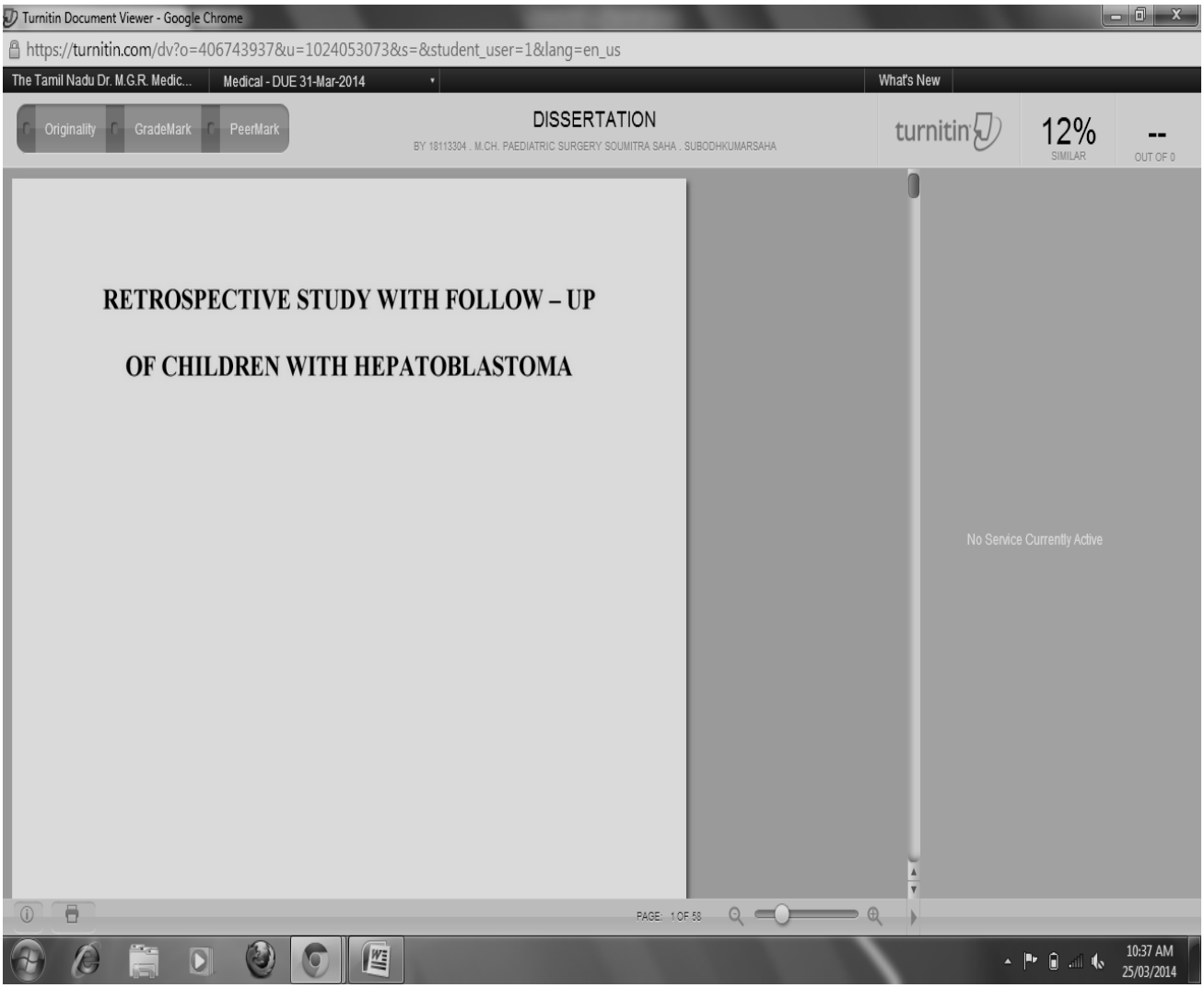
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Retrospective study with follow-up of children with Hepatoblastoma.
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Cc: Dr. Sampath Karl, Paediatric Surgery, CMC.

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ABSTRACT

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Retrospective study with follow up of children with hepatoblastoma.

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DEGREE AND SUBJECT

M.Ch. Paediatric Surgery

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AIMS AND OBJECTIVES

To retrospectively review our single centre experience with neoadjuvant chemotherapy and surgery in hepatoblastoma.

MATERIALS AND METHODS

This is a retrospective study with follow-up of children with hepatoblastoma during the period from January 2003 to December 2012 at Christian Medical College and Hospital, Vellore (CMCH). All 28 (N=28) cases diagnosed and completely treated in CMCH under pediatric

surgery and pediatric oncology were included in this study. Data were retrospectively collected from surgical and medical records. Patient characteristics, mode of diagnosis, treatment modalities, follow-up and disease free survival were analyzed. Data entry was done using Microsoft excel. Data analysis was done using Statistical Package for Social Sciences (SPSS) version 16.

RESULTS

Mean age of presentation was 28.22 months. Male:female ratio was 3.6:1. 27 cases had raised AFP at presentation. Most patients were managed after needle biopsy with 4 cycles of PLADO, surgery and 2 more cycles of PLADO. Among 28 patients, 7 patients did not undergo surgery. 1 patient is disease free after getting full course of chemotherapy without surgery. Remaining 20 patients underwent hepatic resection. There was no intra operative mortality. Among these 20 patients, 13 patients are disease free with near follow-up 3 years. Other 7 patients died.

CONCLUSION

65% patients who underwent hepatic resection are disease free after mean follow-up of approximately 3 years. One patient is disease free after getting full course of chemotherapy without surgery. However 7 patients who were originally seen did not undergo surgery for a variety of reasons making the overall survival 50%.

KEYWORDS: Hepatoblastoma, AFP, PLADO

INTRODUCTION

Hepatoblastoma (HB) accounts around 80% of malignant liver tumor among pediatric age group[1,2]. It is a rare pediatric a pediatric neoplasm. Its incidence is about 1.5 per million. It comprises only about 1% of all pediatric malignancies[3].

Till 1970, surgery was only treatment modality for HB. In the past children with HB were treated with surgery alone and there was around 30% relapse rate. Then we gradually came to know that HB is a chemo sensitive tumor. Tremendous advances in chemotherapy occurred in last 2 decades. In recent era, successful treatment of HB includes neoadjuvant chemotherapy, surgery and adjuvant chemotherapy.

Studies related to HB published in different Indian journals were comparatively dealt with small number of study group and study period as compared to western studies.

This study deals with our experience in the management of hepatoblastoma

AIMS AND OBJECTIVES

Retrospectively review our experience with hepatoblastoma.

REVIEW OF LITERATURE

After neuroblastoma and Wilms' tumor, third most common abdominal neoplasms in pediatric age group is primary tumor of liver [4]. Among primary tumor of liver HB is the most common.

EPIDEMIOLOGY, BIOLOGY, and GENETICS

HB accounts around 80% of malignant liver tumor among pediatric age group[1,2]. It is a rare pediatric a pediatric neoplasm. Its incidence is about 1.5 per million. It comprises only about 1% of all pediatric malignancies[3]. It affects primarily young children between 6 months to 3 years.

Following genetic syndromes are associated with HB and other malignancies[5]:

1. Beckwith – Wiedemann syndrome
2. Li – Fraumeni syndrome
3. Trisomy 18
4. Familial adenomatous polyposis
5. Glycogen storage disease type I-IV

PATHOLOGY

International Society of Pediatric Oncology (Epithelial) liver tumor study group (SIOPEL) classified HB in the following histological subtypes

1. HB, Wholly Epithelial Type
2. Fetal
3. Embryonal / mixed fetal and embryonal
4. Macrotrabecular (MT)
5. Small cell undifferentiated (SCU; formerly anaplastic)
6. HB,Mixed Epithelial and Mesenchymal Type (HB-MEM)
7. Without teratoid features
8. With teratoid features
9. HB, Not Otherwise Specified (HB-NOS)

Prognostically fetal subtype has favorable biology. Macrotrabecular variant (MT) and small cell undifferentiated (SCU) have unfavorable prognosis. MT is difficult to distinguish from hepatocellular carcinoma. SCU is not associated with elevated serum alpha fetoprotein [5,6,7,8,9] .

DIAGNOSIS

Clinical presentation

HB is most commonly seen between 6 months and 3 years of age. It usually presents with right upper quadrant or epigastric mass. Rarely children present with fatigue, anorexia, weight loss, jaundice due to biliary obstruction.

Laboratory evaluation

Routine laboratory investigation

Children with HB may present with thrombocytosis[10,11].

Serum alpha fetoprotein (AFP)

It is the most important tumor marker. It will be elevated in 90% of children with HB. It is the protein produced by fetal liver. Its $t^{1/2}$ is around 7 days. It is present in very high concentrations at birth. Then it rapidly declines to adult levels by 8 months of age. So in infants younger than 8 months, AFP levels must be interpreted carefully. Markedly elevated AFP in a child with a liver mass signifies that the mass is most likely to be HB. Although milder elevation may be seen with mesenchymal hamartoma[12] or tertoma[13]. HB that fails to express (AFP<100 ng/ml) is biologically more aggressive with a poor prognosis.

Radiology

Ultrasonography should be first investigation to know about the organ of origin. Contrast enhanced abdominal computed tomography (CECT) scan will be next radiological investigation. Chest X-ray and CT scan are essential part of initial radiographic evaluation. It will rule out pulmonary metastasis.

PRETEXT, STAGING, AND RISK GROUP STRATIFICATION

PRETEXT stands for pre treatment extent of disease at diagnosis.

POST-TEXT stands for post-treatment extent of tumor after neoadjuvant chemotherapy.

First time the word "PRETEXT" was used by SIOPEL – 1[14].

It divides children with HB under different risk groups. It helps to plan the treatment. It also tells about the outcome.

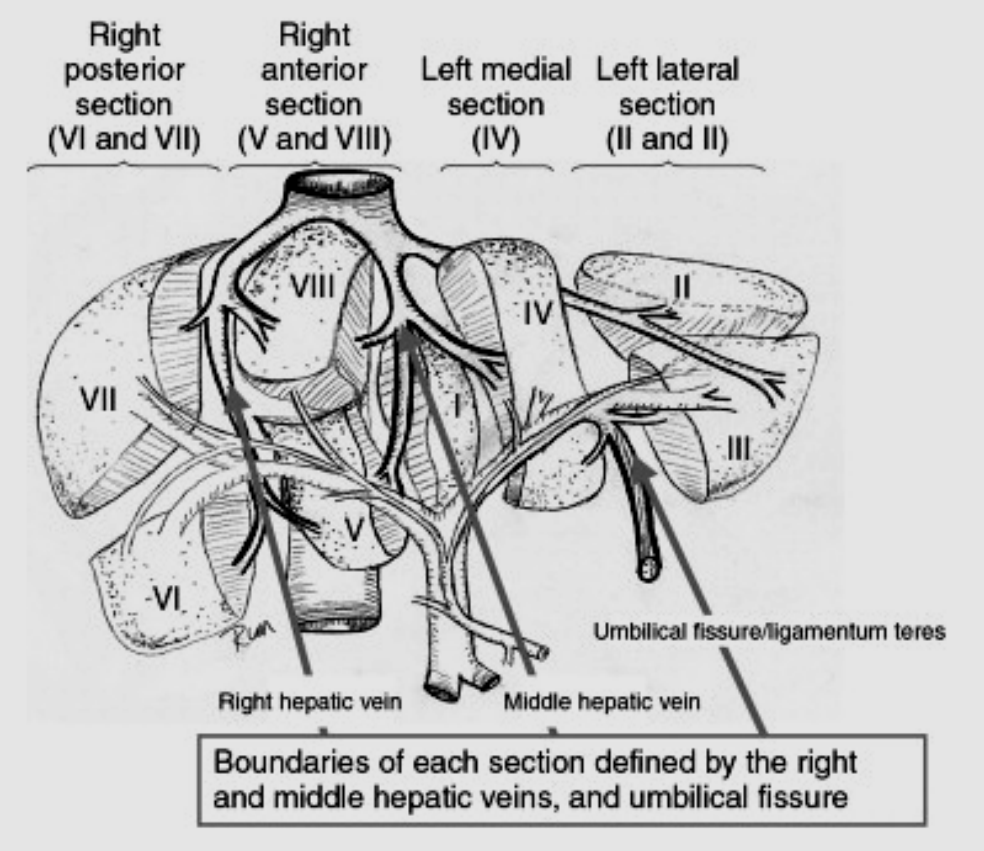


Figure III-1 [5]

PRETEXT system divides liver into four “sections”.

Left lobe of liver: Lateral, Medial section.

Lateral section: Segments II, III.

Medial section: Segment IV.

Right lobe: Anterior, Posterior section.

Anterior section: Segments V, VIII.

Posterior section: Segments VI, VII.

Segment I: Caudate lobe.

PRETEXT
= Extent of tumor at diagnosis

POSTTEXT
= Extent of tumor after neoadjuvant chemotherapy

I ... 3 contiguous sections tumor free
II ... 2 contiguous sections tumor free
III ... 1 contiguous sections tumor free
IV ... no contiguous sections tumor free

In addition, any group may have:
V ... ingrowth vena cava, all 3 hepatic veins
P ... ingrowth portal vein, portal bifurcation
E ... extrahepatic
C ... caudate
M ... metastasis

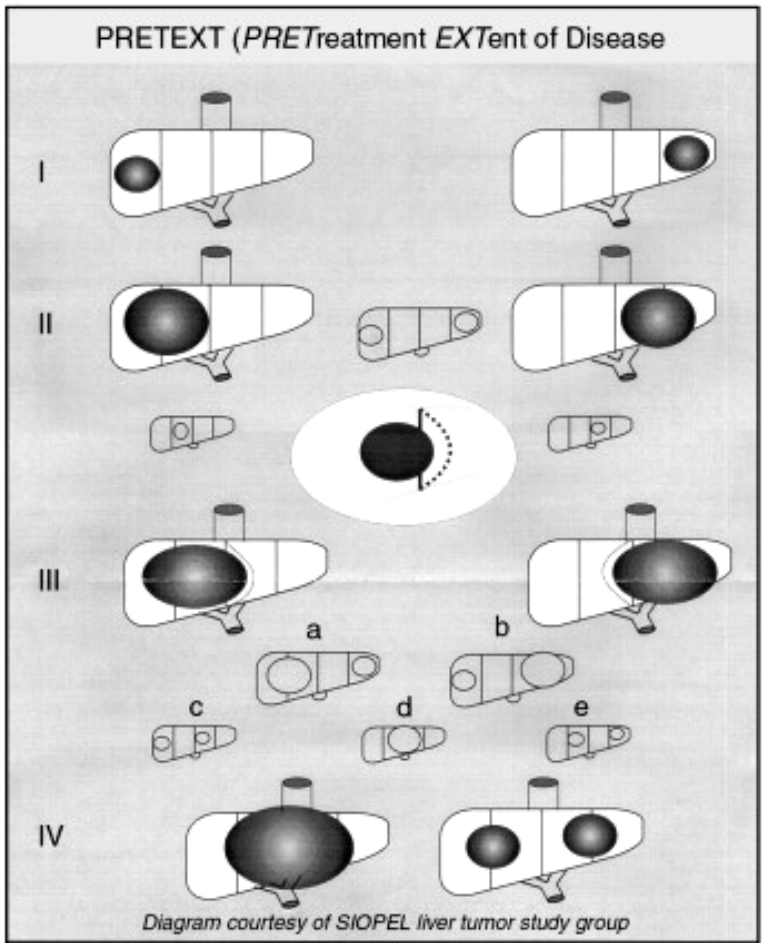


Figure III-2 [5]

V": Involvement of venacava or all three hepatic veins.

"P": Involvement of main portal or both portal branches.

"C": Involvement of caudate lobe.

"E": Extrahepatic contiguous growth (Involvement of diaphragm or stomach).

"M": Distant metastases (mostly lungs) [15].

The Children's Oncology Group (COG) uses traditional COG (Evans) staging system:

Stage I: Complete gross resection at diagnosis with clear margins

Stage II: Complete gross resection at diagnosis with microscopic residual disease at the margins of resection.

Stage III: Biopsy only at diagnosis, or gross total resection with nodal involvement or tumor spill or incomplete resection with gross intrahepatic disease.

Stage IV: Metastatic disease at diagnosis.

There are certain pitfalls of Evans staging system. It relies on resection decision by the sugeon at diagnosis.

Currently COG uses PRETEXT as surgical guidelines [16].

Currently COG stratifies the patients into following risk categories:

Very low risk group:

PRETEXT I / II tumor with pure fetal histology (PFH). Resected margin should be >1cm.

Low risk group:

Any histology with PRETEXT I / II tumor. . Resected margin should be >1cm.

Intermediate risk:

PRETEXT stage III tumor (includes SCU histology).

High risk:

Stage IV tumors

All tumors with AFP level less than 100 ng/ml at diagnosis.

SIOPEL uses PRETEXT for risk stratification. PRETEXT has a tendency to over stage. It can also be used to monitor the tumor following preoperative chemotherapy.

Current SIOPEL Risk Stratification:

Standard risk group:

PRETEXT stage I, II and III tumor

High risk group:

PRETEXT stage IV tumor

Metastasis at the time of diagnosis

SCU histology

AFP level less than 100 ng/ml

TREATMENT STRATEGY, CHEMOTHERAPY, AND SURGERY

It is now clear that surgery alone is not sufficient to cure HB. Since 1970, evidences were started accumulating regarding chemosensitive nature of HB. In 1980, there was a major impact on survival following introduction of cisplatin and doxorubicin. Now cisplatin became the backbone of chemotherapy.

Advantages of neoadjuvant (preoperative) chemotherapy:

1. It reduces the tumor volume

2. It makes the tumor more solid and better demarcated from remaining liver. There is also less intraoperative bleeding.

3. It makes the tumor resectable, reduces surgical morbidity. It provides more time to make plans like liver transplantation.

4. Lung metastases may completely disappear following neoadjuvant chemotherapy.

Every HB child should receive neoadjuvant chemotherapy. Cisplatin monotherapy is comparable with cisplatin/doxorubicin combination chemotherapy (PLADO) in the treatment of PRETEXT I, II and III tumor [17].

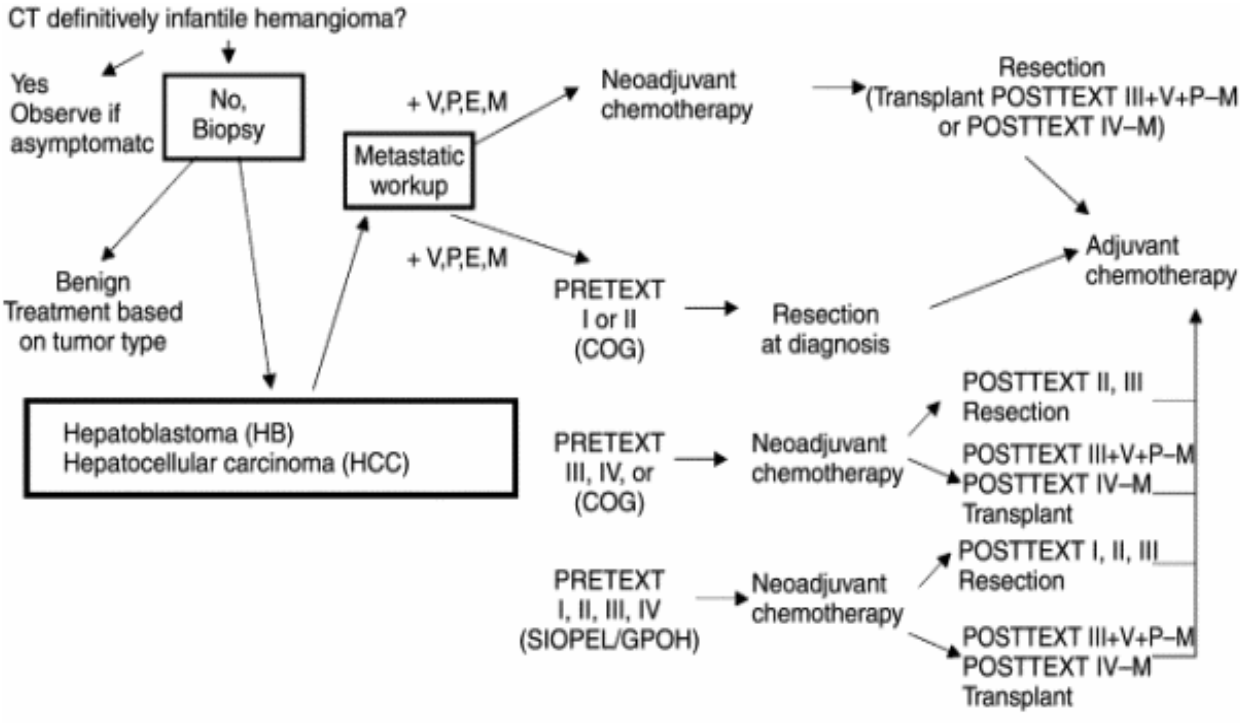


Figure III-3 [5]

Similar to SIOPEL, GPOH study group in their recent trial (HB 99) concluded neoadjuvant chemotherapy should be given in all patients [6,19].

COG study group in their recent trial (AHEP-0731) concludes PRETEXT I and II tumor should be resected at diagnosis with 1 cm of margin. Best option for POSTTEXT III d central tumor is

mesohepatectomy. Transplantation is preferred option if any tumor involving major vascular inflow or outflow [7,17] .

Currently postoperative (adjuvant) chemotherapy is recommended by all study group. The backbone of all chemotherapy regimen is cisplatin. But there is one small exception.

According to COG AHEP-0731 no chemotherapy is required for pure PFH children those underwent resection at diagnosis [10,20,21] .

Currently COG uses the following chemotherapy regimen:

Low-risk tumors: Cisplatin / 5FU (Fluorouracil) / Vincristine (C5V).

Intermediate-risk tumor: C5V + Doxorubicin.

High-risk tumor: New agents (Irinotecan) will be investigated with upfront window therapy[22].

Cisplatin monotherapy with PLADO was compared in SIOPEL3 [23]. In SIOPEL3 only SUPERPLADO (Cisplatin / Carboplatin / Doxorubicin) was used for high-risk group[18]. In the current SIOPEL4, for high-risk group, dose-dense cisplatin-based chemotherapy is being used [24].

In the GPOH trial (Hepatoblastoma 94), Ifosfamide, Cisplatin and Doxorubicin) were used[8].

In the GPOH trial (Hepatoblastoma 99), IPA was used for standard risk and CARBO/VP16 (Caboplatin/Etoposide) was used for high risk[19].

In the Japanese trial, Cisplatin and Pirarubicin were used to treat standard risk.

In the same trial ITEC (Ifosfamide/Pirarubicin/Etoposide/Carboplatin) + HACE (Hepatic artery chemoembolilization) were used for high-risk patients[25].

In both North America and Europe, irinotecan ± doxorubicin, has been used for patients with relapse[26,27].

Following important conclusions were mentioned in SIOPEL 3:

1. Using standard treatment, around 25% of patients who present with metastasis are finally cured.
2. Alternative chemotherapy and surgical resection should be thought to treat pulmonary metastasis when there was no response following chemo.
3. Microscopic positive margin following resection may not be a poor prognostic factor when there is excellent response following chemo.
4. Liver transplantation or major resection should be considered in unresectable hepatoblastoma [28,29,31,32,33].

In the COG trial, AHEP-0731, following decisions were made:

1. Very-low-risk patients with PFH should be resected at presentation without any chemotherapy.

2. Low-risk patients with non-PFH should be resected at diagnosis and followed by 2 cycles of C5V

3. Intermediate-risk group patients with stage I and II SCU, or any stage III HB should receive doxorubicin in addition to C5V therapy.

4. High-risk patients with metastasis at presentation or initial AFP < 100ng/ml should be treated with irinotecan followed by C5VD.

Liver transplantation for hepatoblastoma:

Due to availability of effective chemotherapy, children with unresectable HB can undergo total liver resection followed by orthotopic liver transplantation (OLT) [35].

Transplantation outcomes for hepatoblastoma:

Overall survival at 10 years following primary transplantation was around 85%. But it was dropped into 40% when children underwent rescue transplantation[36].

Indications and contraindications for OLT:

a) Multifocal PRETEXT IV tumor at diagnosis.

b) Unifocal PRETEXT IV tumor at diagnosis.

c) POSTTEXT III tumor involving major vascular outflow.

d) POSTTEXT III tumor involving major vascular inflow.

e) Rescue Transplantation [37,38].

Transplantation versus Extreme resection:

Among transplantation and extreme resection, later is the better option for avoiding long-term immunosuppression. Extensive resection, with vessels reconstruction should be done by expert surgical team [39,40,41].

Transplantation in HB child with lung metastasis at presentation:

Absolute contraindication:

a) Persistent lung metastases which are non-responsive to chemotherapy.

b) Lung metastases which are difficult for surgical resection.

Relative contraindication:

Lung metastases which are stable or progressive disease following preoperative chemotherapy.

If the lung has >4 nodules in the same lobe, lobectomy is preferable rather than metastatectomy[42].

Rescue transplantation in local relapse:

In comparision with rescue transplantation there is always superior outcome following primary transplantation.

Live-donar liver transplantation (**LDLT**) is the new trend [36,43,44].

PLUTO:

Full form is Pediatric Liver Unresectable Tumor Observatory

It is a worldwide electronic registry for liver transplantation[45]. The website of registry is http://pluto.cineca.org/access.

Hepatic arterial chemoembolisation and Transarterial chemoembolisation [46]:

This technique is quite popular in China.

Chemotherapeutic drugs have used in various combination of cisplatin, doxorubicin, vincristine, pirarubicin, mitomycin etc.

Most often it is used as a palliative care.

Cisplatin related hearing problem:

This is more common in children younger than 5 years of age. There is high frequency hearing loss.

COG AHEP 0731 trial is trying to decrease the dose of cisplatin in low-risk group [47,48].

Childhood Hepatic Tumor International Collaboration (CHIC):

This trans-atlantic development is eventually going to benefit children with liver tumor.

Prognosis for recurrent or progressive HB depends on following factors:

1. Site of recurrence
2. Prior treatment
3. Multidrug chemotherapy resistance
4. Individual patient consideration

MATERIALS AND METHODS

STUDY DESIGN AND STUDY DESIGN

This is a retrospective study with follow-up of children with hepatoblastoma during the period from January 2003 to December 2012 at Christian Medical College and Hospital, Vellore (CMCH). All the children who came under pediatric surgery and pediatric oncology were included in this study.

STUDY PERIOD

The study has been done over a period of ten years (January2003 - December 2012).

SAMPLE SIZE

Hepatoblastoma is a rare pediatric a pediatric neoplasm. Its incidence is about 1.5 per million. So all 28 (N=28) cases diagnosed and completely treated in CMCH under pediatric surgery and pediatric oncology were included in this study.

INCLUSION CRITERIA

All children who were diagnosed and treated in CMCH under pediatric surgery and pediatric oncology.

EXCLUSION CRITERIA

Children with age above 15 years were excluded from the study.

DATA COLLECTION

Data were retrospectively collected from surgical and medical records. Patients' contact addresses and phone numbers were also collected from medical records and they were invited to visit hospital for follow-up.

This included sex, age at presentation, mode of presentation, mode of diagnosis, histopathological types, alpha-fetoprotein (AFP) level at presentation, β-HCG level at presentation, liver function test (LFT), creatinine, pulmonary and other metastasis at presentation, PRETEXT (Pretreatment extent of disease) staging, number of PLADO cycles or any other chemotherapeutic drugs used as neoadjuvant chemotherapy, POSTTEXT (Posttreatment extent of disease) staging before surgery, AFP level just before surgery, types of hepatectomy, reasons behind not undergoing hepatectomy, number of PLADO cycles or any other chemotherapeutic drugs used as adjuvant chemotherapy, recurrences and metastasis

following primary treatment, any redosurgeries, disease free survival, AFP at last follow-up, any deaths during follow-up.

STATISTICAL METHODS

Data entry was done using Microsoft excel.

CONSENT AND APPROVAL

Aim and purpose of the study were informed to the parents and children and their informed consents were obtained. The data collection was done after obtaining approval from Unit Heads of Department of Paediatric Surgery, Pathology, Radiology, Paediatric Oncology and Medical Records Department, Christian Medical College and Hospital, Vellore. Participants' identify and all the data were kept confidential.

RESULTS AND ANALYSIS

CHARACTERISTICS OF STUDY POPULATION (N=28)

Total number of children who were diagnosed and treated in CMCH under pediatric surgery and pediatric oncology during the period from January 2003 to December 2012 was 28.

SEX RATIO

Among 28 children, 22 were male and 6 were female (3.6:1).

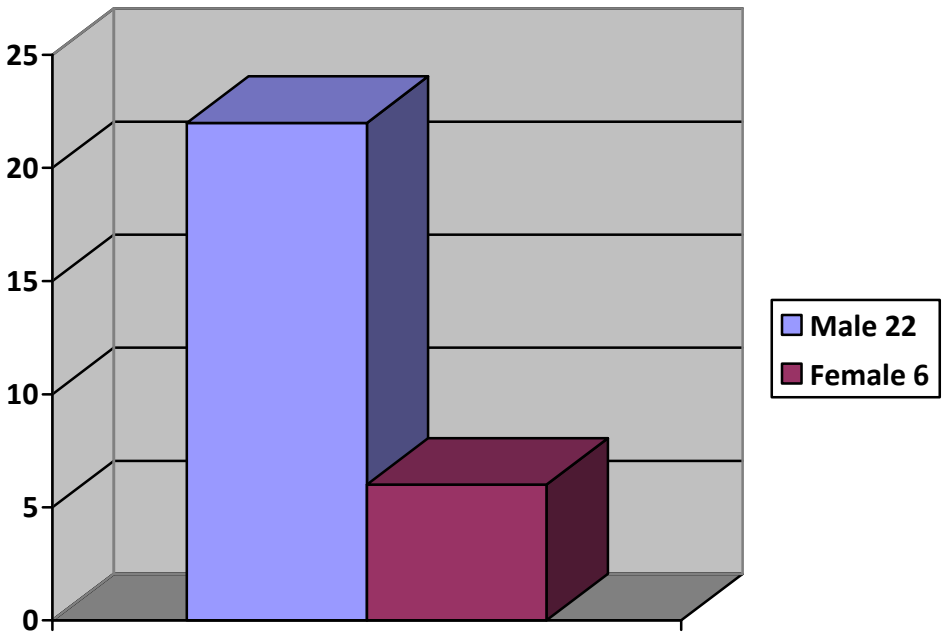


FIGURE V-1 Sex ratio

AVERAGE AGE OF PRESENTATION

Average age of presentation was 28.22 months.

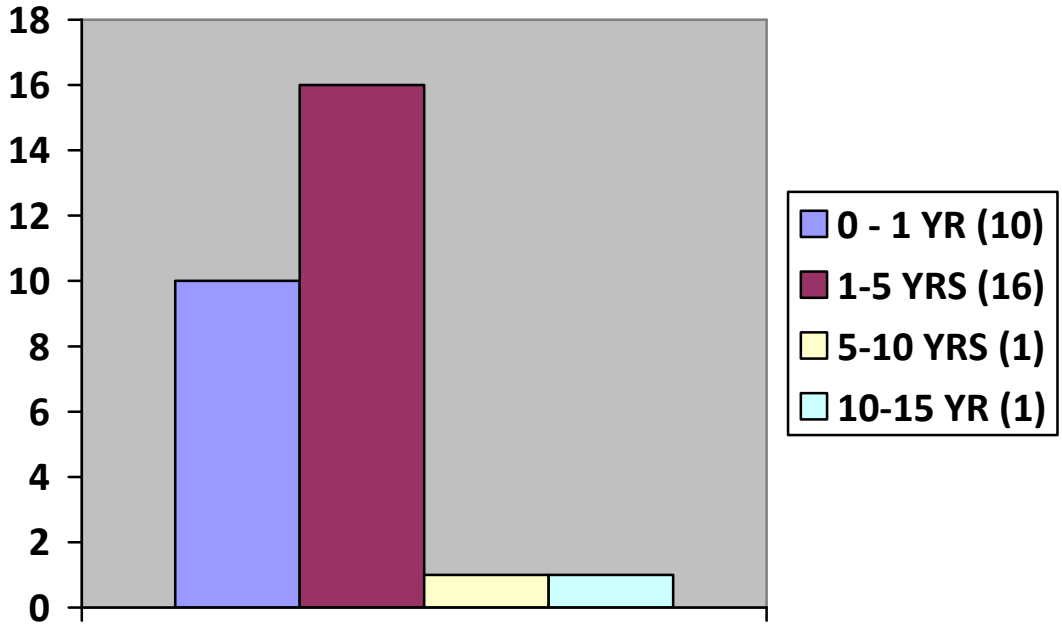


FIGURE V-2 Average age of presentation

MODE OF PRESENTATION

All 28 patients presented with abdominal mass. Along with abdominal mass 3 presented with jaundice and 1 presented with male isosexual precocious puberty.

MODE OF DIAGOSIS

Among 28 children, 23 (82.14%) were underwent trucut biopsy. Without biopsy, on the basis of CT findings and raised AFP, 4 (14.28%) were diagnosed to have hepatoblastoma. Only 1 child (3.57%) underwent open biopsy for diagnosis.

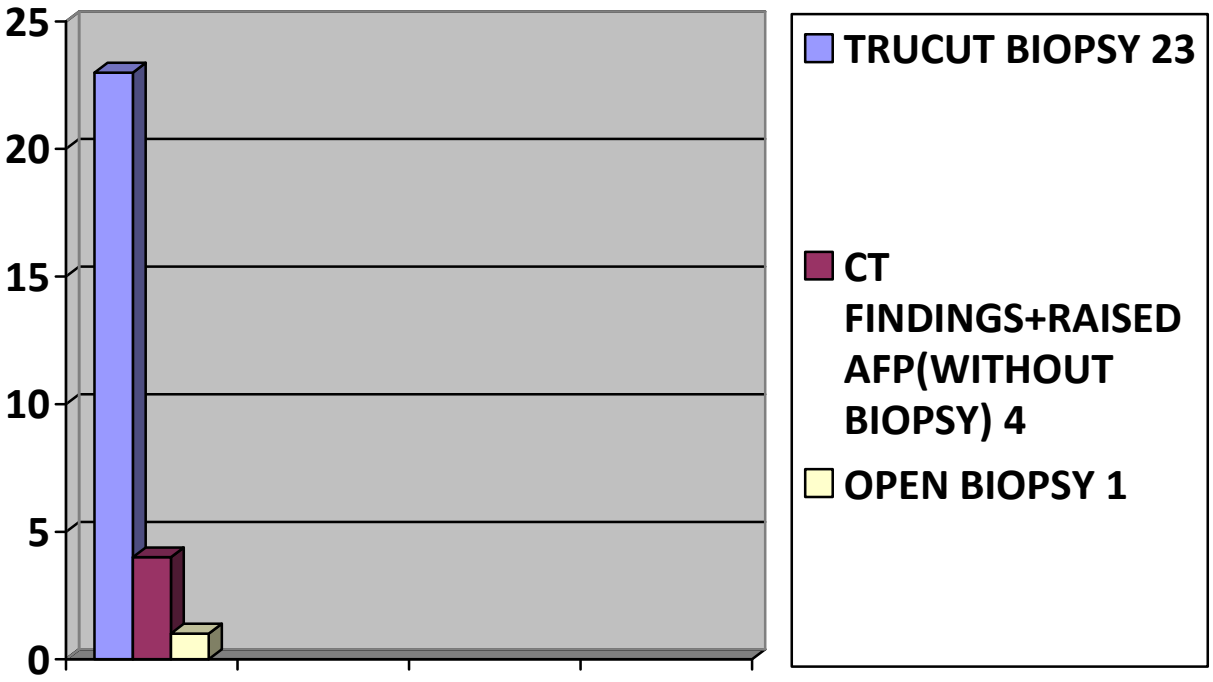


FIGURE V-3 MODE OF DIAGNOSIS

HEPATOBLASTOMA HISTOLOGICAL SUBTYPES

Among 28 children, 17 patients had epithelial variety (60.71%). Among these, one had small cell undifferentiated and one had macrotrabecular subtypes. Another child developed macrotrabecular type of metastasis. Prognostically both small cell undifferentiated and macrotrabecular variants have unfavorable biology.

Remaining, 11 children had mixed epithelial and mesenchymal type (39.28%).

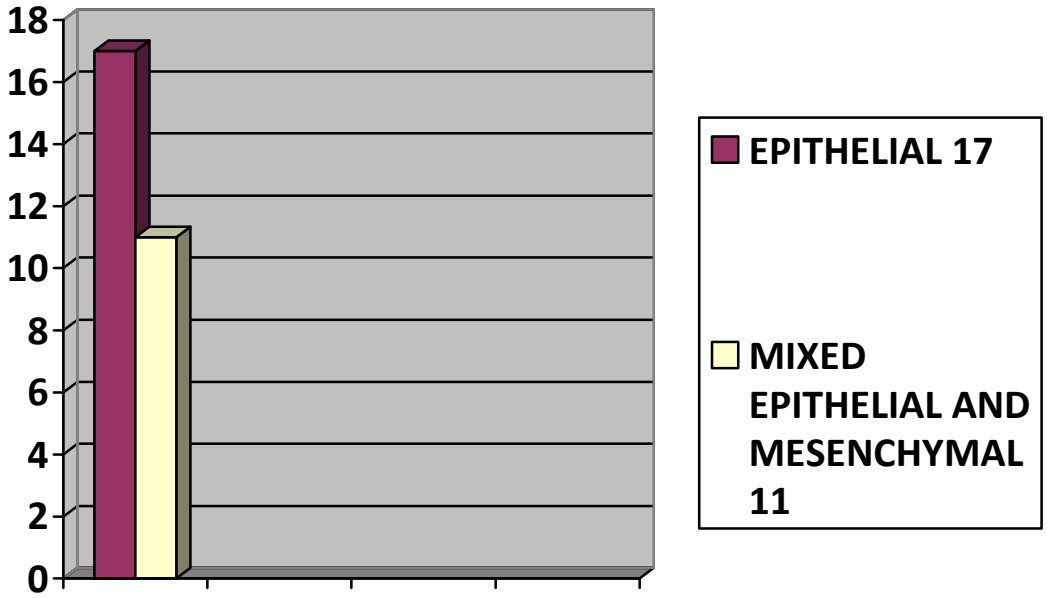


FIGURE V-3 Hepatoblastoma histological subtypes

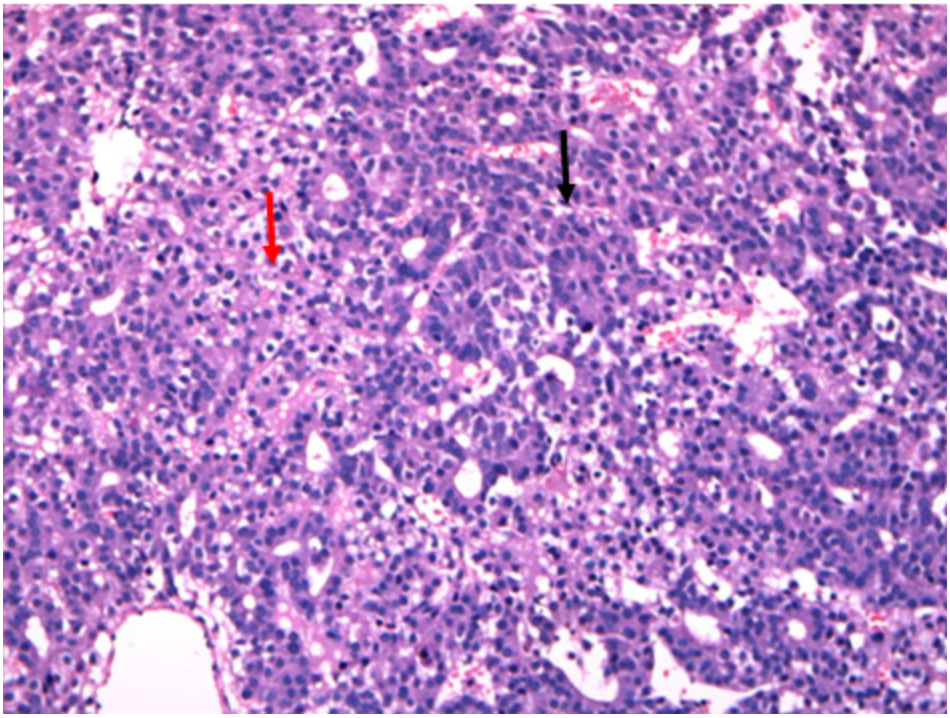


FIGURE V-4 Hepatoblastoma, epithelial type. Black arrow – embryonal. Red arrow – fetal. H&E 20x.

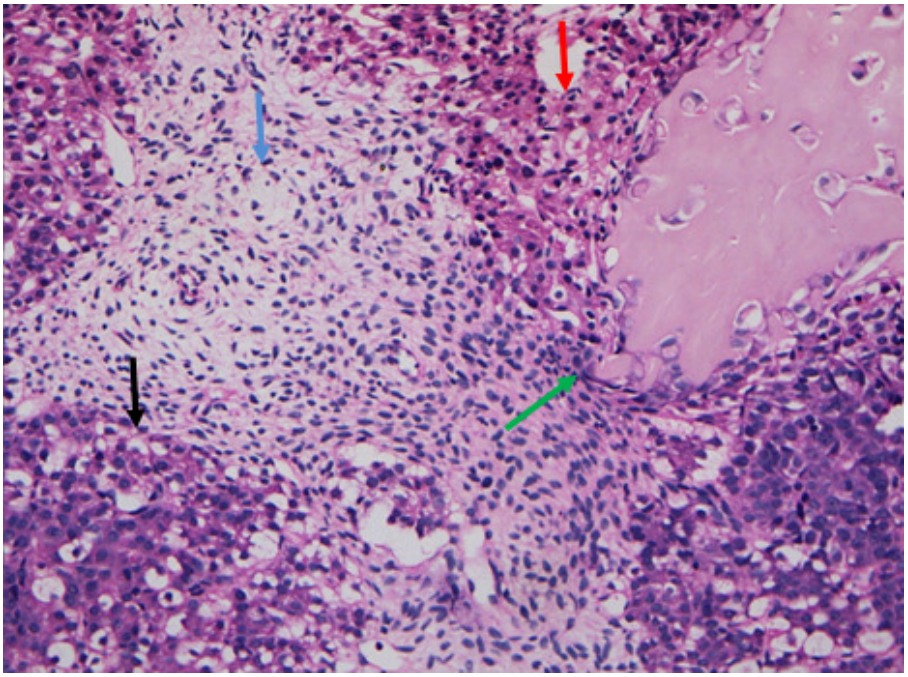


FIGURE V-5 Hepatoblastoma, mixed epithelial and mesenchymal. Black arrow – embryonal. Red arrow – fetal. Green arrow – osteoid. Blue arrow – immature mesenchyme. H&E 20x.

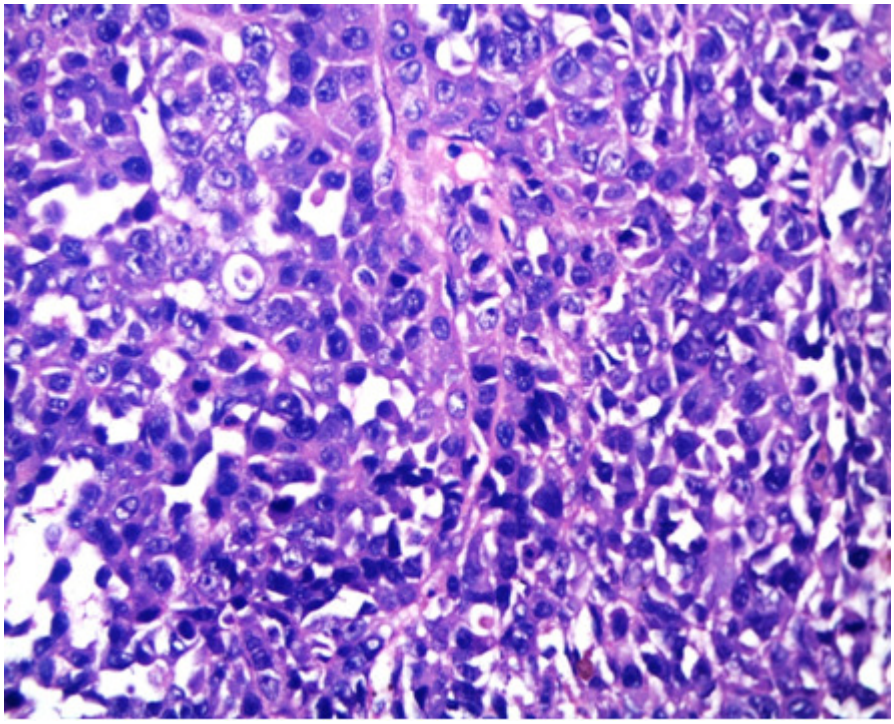


FIGURE V-6 Hepatoblastoma, teratoid type. Epithelial elements. H&E 40x.

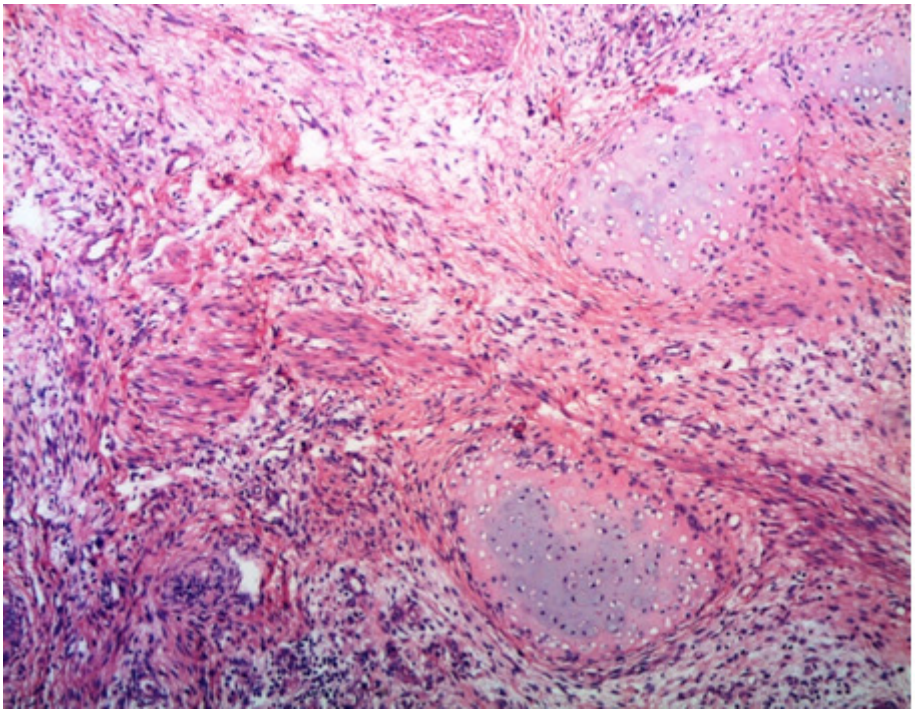


FIGURE V-7 Hepatoblastoma, teratoid type. Cartilage and smooth muscle bundles. H&E 10x

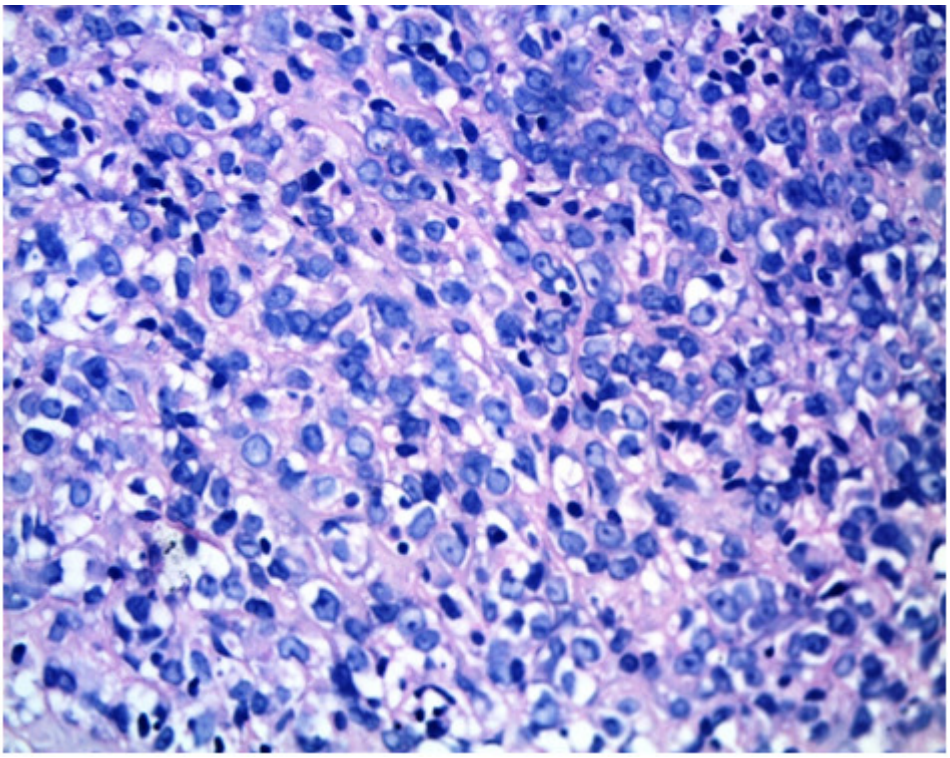


FIGURE V-8 Hepatoblastoma, undifferentiated type. H&E 40x

AFP AT PRESENTATION (IU/ml)

Normal value is up to 5.5 IU/ml. Among 28 children, only 1 child presented with 4.32 IU/ml AFP level and tumor subtype was small cell undifferentiated hepatoblastoma. Remaining 27 children presented with >100 IU/ml AFP level (Max. value 3500000 IU/ml).

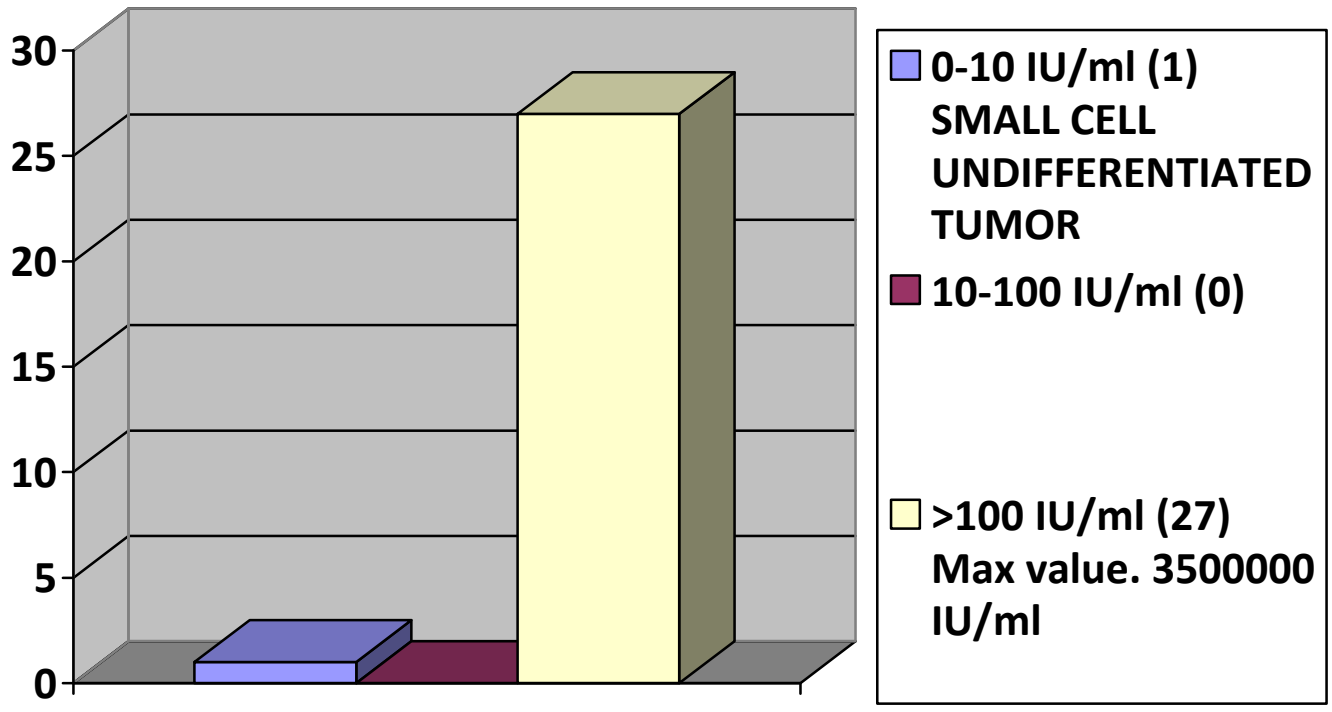


FIGURE V-9 AFP level (IU/ml) at presentation

ELEVATED β-HCG (mIU/ml) AT PRESENTATION

Among 28 children, 1 boy and 1 girl presented with high β-HCG (mIU/ml) level. Normal β-HCG level is up to 5.0 mIU/ml. Both of them died.

No. of patients	B-HCG level at presentation (mIU/ml)
1 boy	167 mIU/ml
1 girl	17.11 mIU/ml

FIGURE V-10 BOY WITH HIGH β-HCG & MALE ISOSEXUAL PRECOCIOUS PUBERTY (ENLARGED PENIS)

LIVER FUNCTION TEST (LFT) & CREATININE AT THE TIME OF PRESENTATION

Among 28 children, 3 presented with abnormal LFT with raised total and direct bilirubin. On the other hand, all had normal creatinine at beginning.

METASTASIS AT PRESENTATION

Among 28 children, 2 presented with multiple lung metestastasis.

FIGURE V-11 Multiple lung metastasis at presentation

NEOADJUVANT (PREOPERATIVE CHEMOTHERAPY)

Preoperatively all 28 patients received neoadjuvant chemotherapy. On an average the patients received 4 cycles of PLADO (cisplatin/doxorubicin combination chemotherapy), ranging from 2 to 6 cycles.

Following 2 cycles of PLADO regimen, one child received 7 cycles JEB regimen (Carboplatin, Etoposide, Bleomycin).

One boy received 3 cycles of PLADO at the beginning. There was no significance response, hence his treatment was individualized to IVA (Vincristine, Actinomycin, Ifosfamide) alternate with JEB (Carboplatin, Etoposide, Bleomycin).

Another boy received 4 cycles of PLADO followed by rapid COJEC protocol (Vincristine, Carboplatin, Etoposide, Cyclophosphamide) due to simultaneous presentation of hepatoblastoma and right paravertebral neuroblastoma.

SIMULTANEOUS PRESENTATION OF HEPATOBLASTOMA & NEUROBLASTOMA

FIGURE V-12 Hepatoblastoma (II V0 P0 E0 C0 M0)

FIGURE V-13 Right paravertebral Neuroblastom

Child was treated successfully

AFP LEVEL (IU/ml) LEVL AFTER NEOADJUVANT CHEMOTHERAPY

Child with small cell undifferentiated tumor had AFP value of 2.68 IU/ml. Following neoadjuvant chemotherapy AFP value of 4 children came down within 10 to 100 IU/ml. The AFP values of remaining 23 children were between 100 IU/ml and 30000 IU/ml).

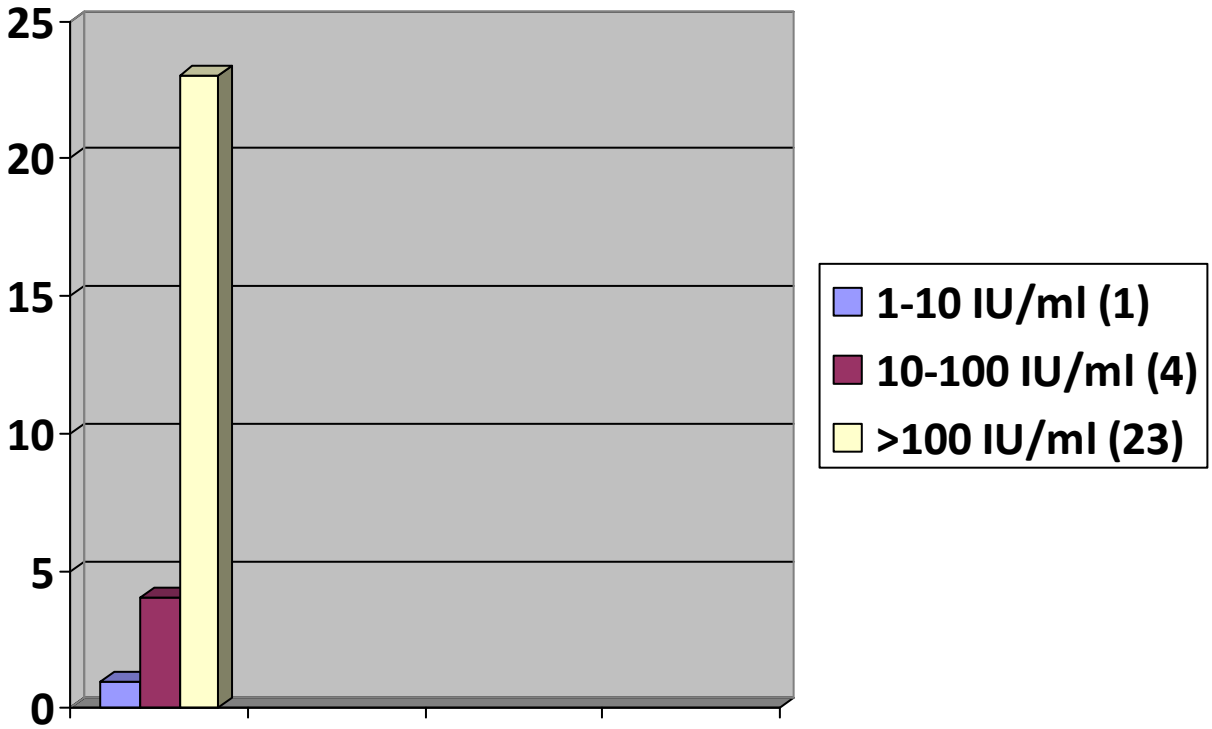


FIGURE V-14 AFP level (IU/ml) after neoadjuvant chemotherapy

PRETEXT AND POSTTEXT STAGING

Among 28 patients, PRETEXT and POSTTEXT staging were done on 25 patients. PRETEXT staging distribution was as follows; PRETEXT Stage I 16% (n=4), Stage II 48% (n=12), Stage III 24% (n=6), and Stage IV 12% (n=3).

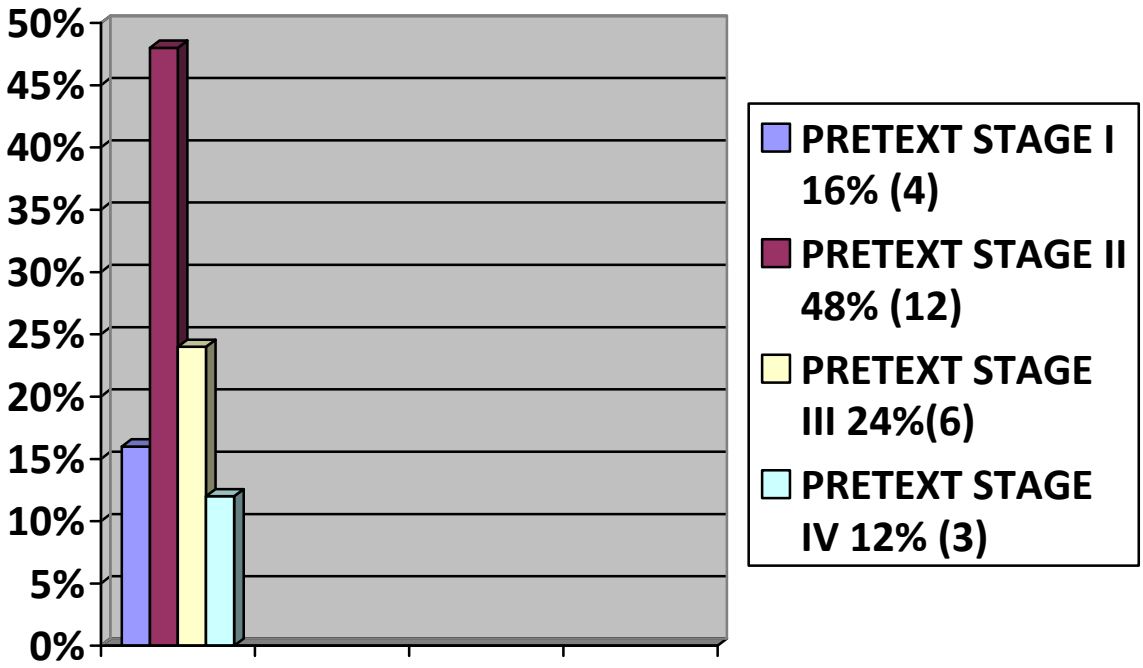


FIGURE V-15 PRETEXT Staging

FIGURE V-16 [Top] PRETEXT (III) and [Bottom] POSTTEXT (III) of the same child. Child underwent right hemihepatectomy.

FIGURE V- 17 [Top] PRETEXT (II V0 P0 E0 C0 M0) and [Bottom] POSTTEXT (II V0 P0 E0 C0 M0) of the same child. Child underwent nonanatomic resection.

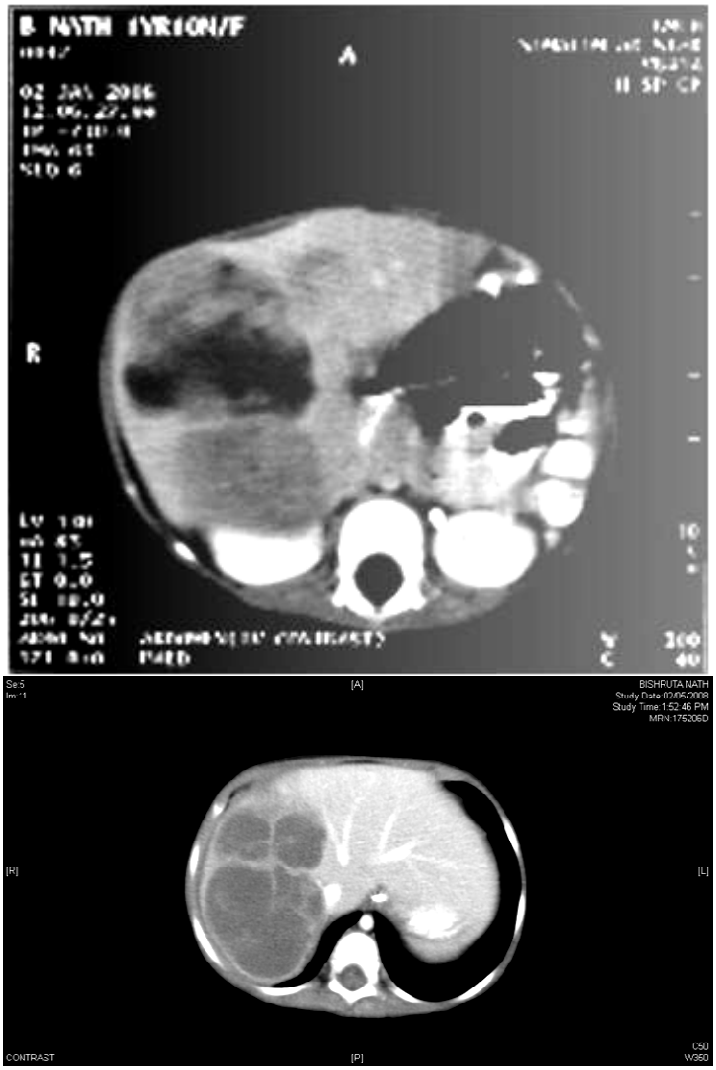


FIGURE V-18 [Top] PRETEXT (IIV0P0E0C0M0) and [Bottom] POSTTEXT (IIV0P0E0C0M0) of the same child.

Child underwent right hemihepatectomy.

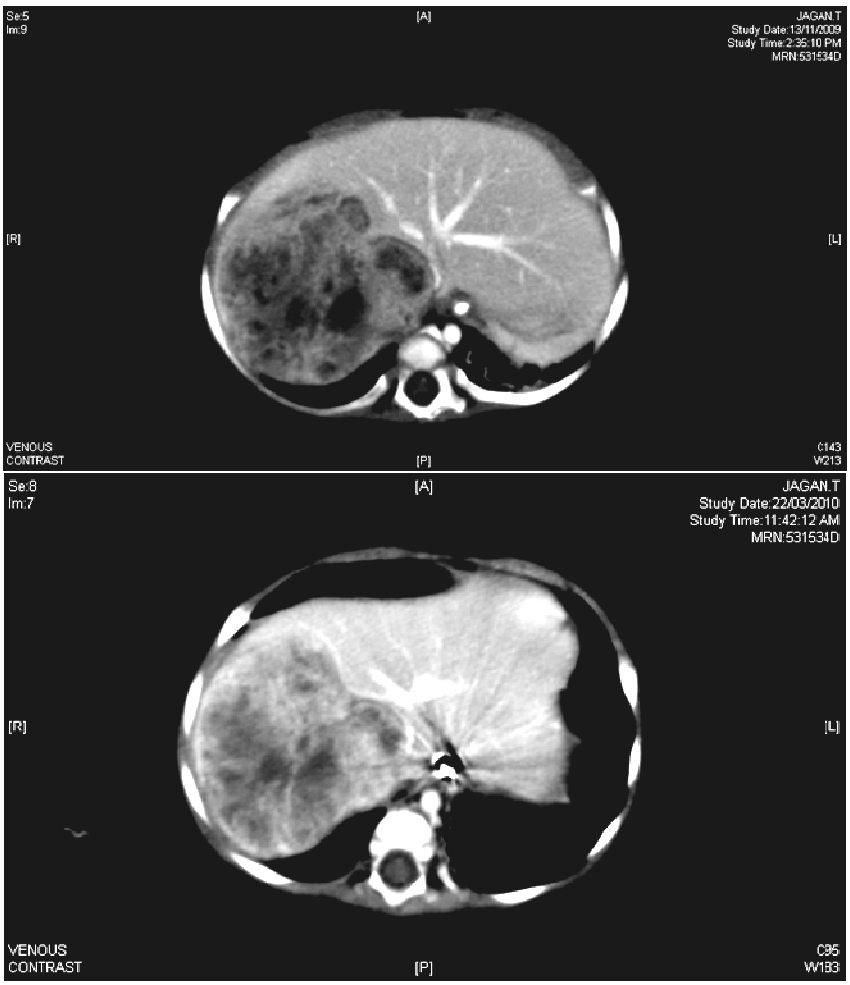


FIGURE V- 19 [Top] PRETEXT (IIV0P0E+C0M0) and [Bottom] POSTTEXT (IIV0P0E+C0M0) of the same child.

Not much response in respect to size. Child underwent right hemihepatectomy

FIGURE V- 20 [Top] PRETEXT (I V0 P+ E0 C0 M0) and [Bottom] POSTTEXT (I V0 P+ E0 C0 M0) of the same child. Child underwent left hemihepatectomy.

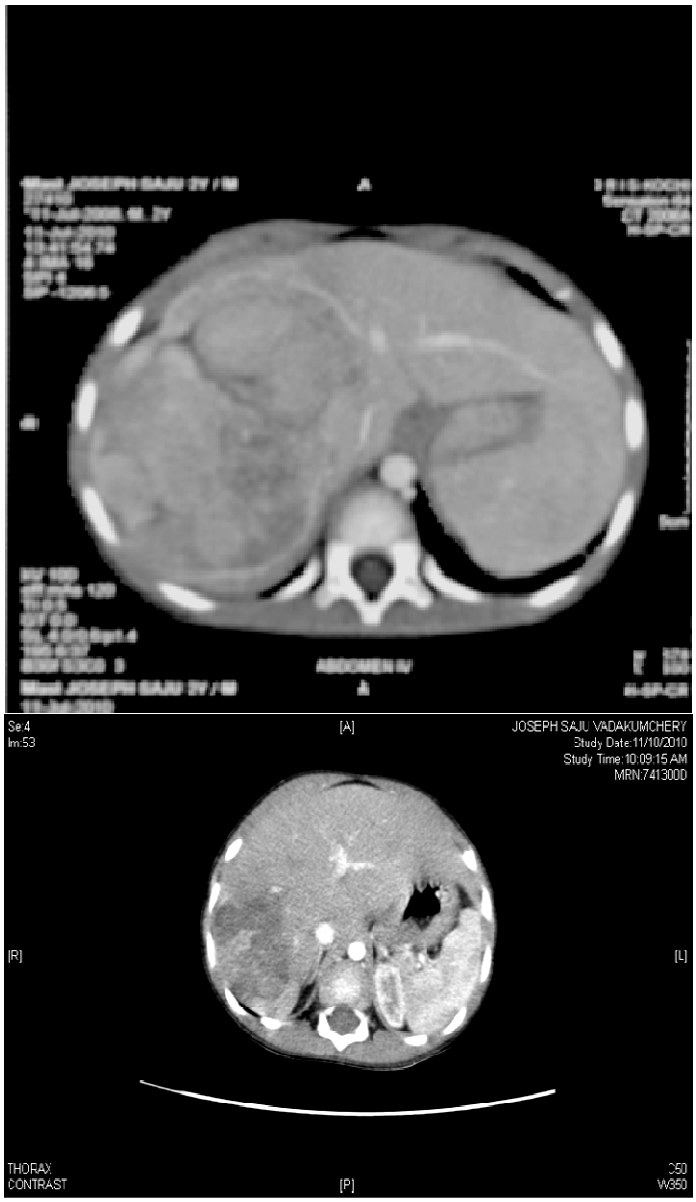


FIGURE V- 21 [Top] PRETEXT (II V0 P+ E0 C0 M+) and [Bottom] POSTTEXT (II V0 P0 E0 C0 M0) of the same child. Child underwent right hemihepatectomy.

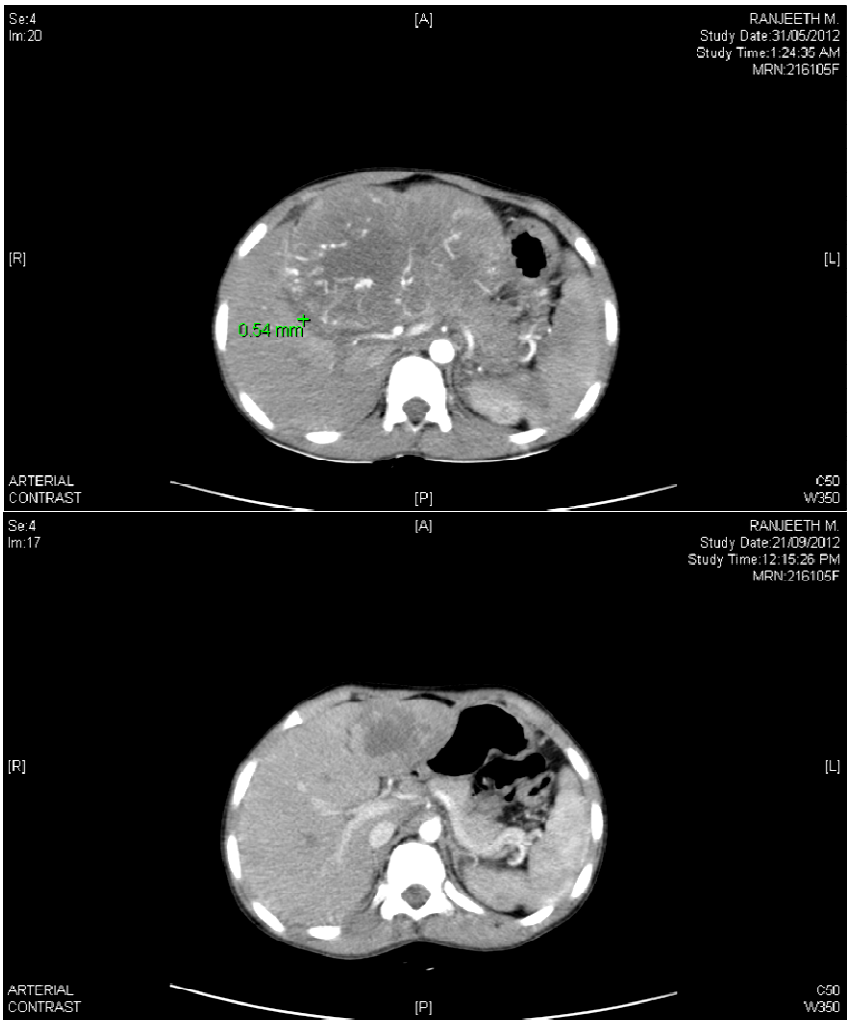


FIGURE V- 22 [Top] PRETEXT (II V0 P0 E0 C0 M0) and [Bottom] POSTTEXT (I V0 P0 E0 C0 M0) of the same child. Child underwent left hemihepatectomy.

HEPATECTOMY

Among 28 (N=28) patients, 20 patients underwent hepatic resection (71.42%). Remaining 7 patients did not undergo surgery. Extensive residual disease with metastasis was the major reason behind this.

TYPES OF HEPATECTOMY

Among 20 patients, 7 underwent right hemihepatectomy, 3 underwent right trisectionectomy, 4 were treated with left hemihepatectomy, only 1 underwent left lateral sectionectomy and remaining 5 children underwent segmentectomy.

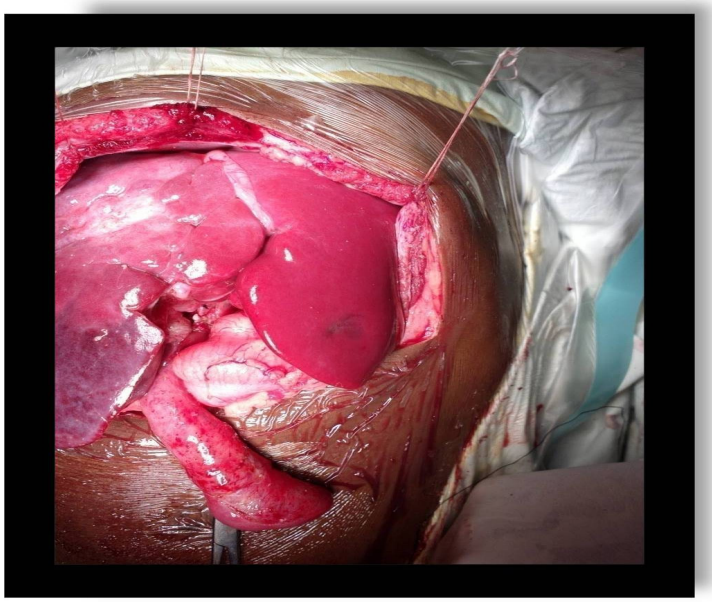


FIGURE V-23 Child successfully underwent right trisectionectomy

ADJUVANT CHEMOTHERAPY

Postoperatively on an average children received 2 cycles of cisplatin and doxorubicin (PLADO).

SPECIAL SITUATION

One patient seems cured with chemotherapy alone. This 3 years girl presented with exomphalos and the liver mass was protruding through it. At presentation AFP was 856 IU/ml. The tumor was central in location and PRETEXT stage was III. 6 cycles of PLADO were given. POSTTEXT stage was III. Recent AFP value was 0.596 IU/ml. PET-CT was done and showing no tumor activity. Disease free survival was 10 months.

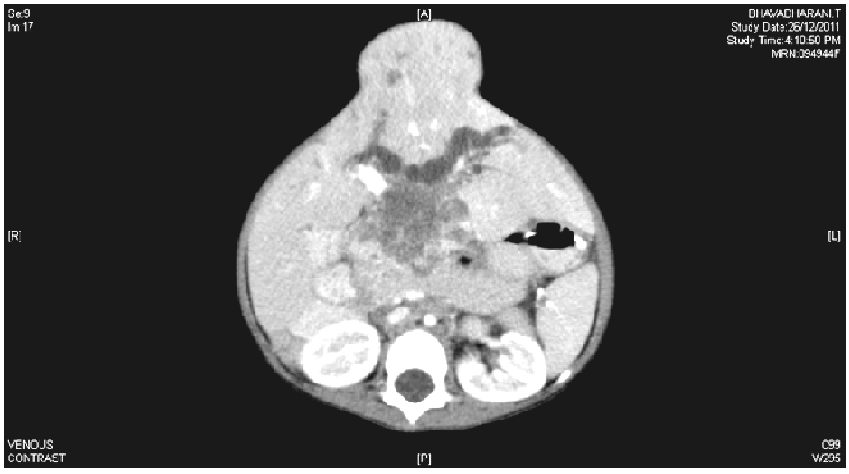


FIGURE V-24 AT PRESENTATION (PRETEXT II V0 P+ E+ C0 M0)

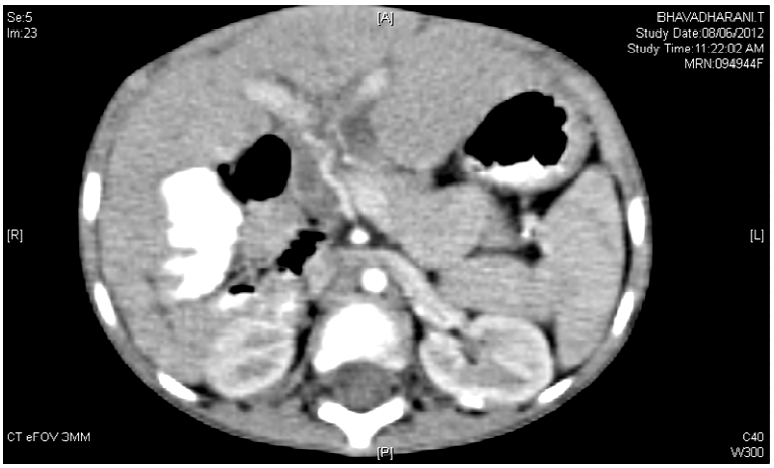


FIGURE V-25 POSTTEXT (II V0 P+ E+ C0 M0)

FIGURE V-26 PET-CT. NO RESIDUAL DISEASE.

TUMOR RELAPSE

Among 28 children, 4 had recurrent disease at remaining liver tissue and 3 had distant metastasis at lung, brain and skull. All 7 patients died.

FIGURE V-27 Recurrence at segment V, status left hepatectomy.

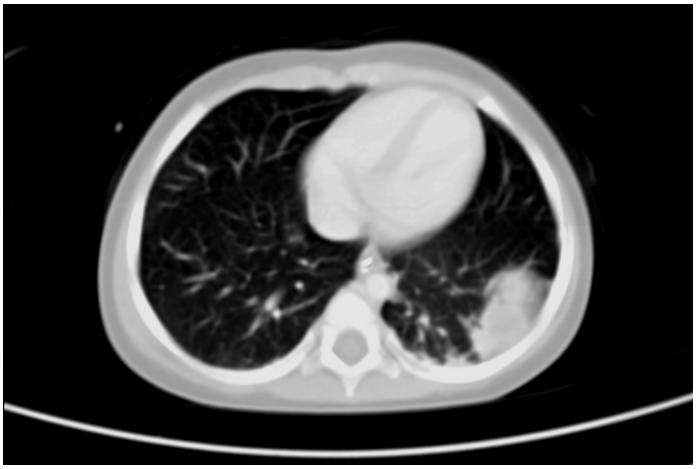


FIGURE V-28 Metastasis at left lower lobe of lung.

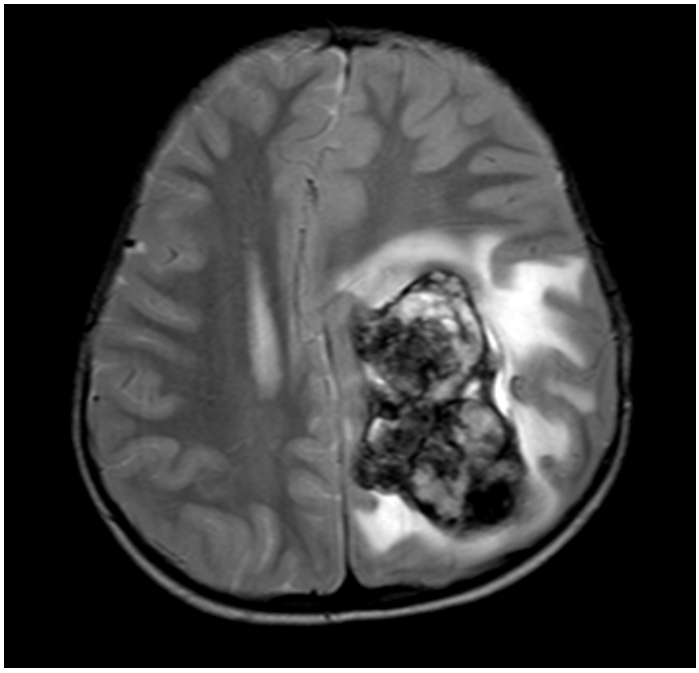


FIGURE V-29 Metastasis at left fronto-parietal lobe.

SURVIVAL ACCORDING TO PRETEXT STAGE

The overall survival according to the PRETEXT stage was as follows: PRETEXT I 50%, PRETEXT II 91.66%, PRETEXT III 16.66% and PRETEXT IV 0%.

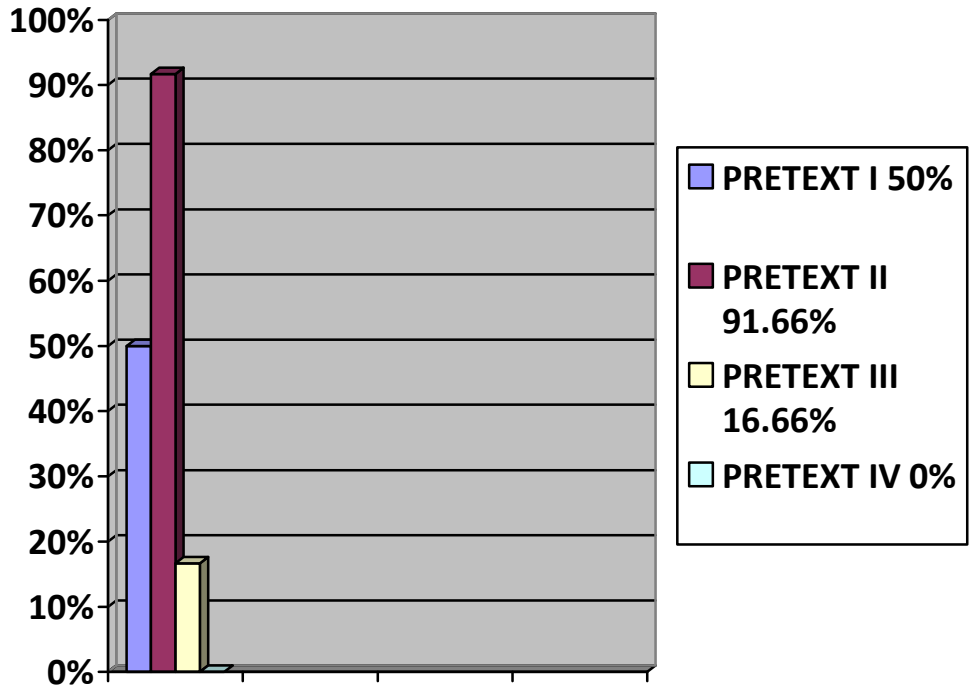


FIGURE V-30 Survival according to PRETEXT stage

OUTCOME

- Among 28 patients, 7 patients did not undergo surgery because of extensive residual disease with metastasis.
- 1 patient is disease free after getting full course of chemotherapy without surgery.
- Remaining 20 patients underwent hepatic resection. There was no intra operative mortality. Among these 20 patients, 13 patients are disease free with near follow-up 3 years. Other 7 patients died.

DISCUSSION

Hepatoblastoma accounts around 80% of malignant liver tumors among pediatric age group[1,2]. Till 1970, surgery was only treatment modality for HB. In the past children with HB were treated with surgery alone and there was around 30% relapse rate. Then we gradually came to know that HB is a chemo sensitive tumor. Tremendous advances in chemotherapy occurred in last 2 decades. In recent era, successful treatment of HB includes neoadjuvant chemotherapy, surgery and adjuvant chemotherapy.

This is a retrospective study with follow-up of children with hepatoblastoma during the period from January 2003 to December 2012 at Christian Medical College and Hospital, Vellore (CMCH). All 28 children (N=28) who came under pediatric surgery and pediatric oncology were included in this study.

In our study, average age of presentation was 28.22 months and 57.14% of children belonged to 1-5 years of age group. Male: female ratio was 3.6:1 and it was compared to some of the previous reports. All 28 children presented with abdominal mass. 3 of them presented with jaundice due to central quadrant tumor and 1 with male isosexual precocious puberty.

Trucut biopsy (82.14%) was the commonest mode of diagnosis. 14.28% children were diagnosed on the basis of CT findings and raised AFP. One child (3.57%) had undergone open biopsy.

HB with low AFP at diagnosis will have extensive disease, poor response to chemo, and also poor outcome [49]. In our study, 1 child with small cell undifferentiated (SCU; formerly anaplastic)

subtype presented with low AFP value (4.32 IU/ml) at presentation. All the others presented with >100 IU/ml AFP (Max. value 3500000 IU/ml).

Survival is influenced by histopathological subtypes. Fetal subtype has favorable prognosis. But small cell undifferentiated and macrotrabecular variant have unfavorable outcome [6,50]. In our study 60.71% was epithelial variety and 39.28% was mixed epithelial and mesenchymal type. One child had small cell undifferentiated tumor and another child had macrotrabecular subtype. Both of them died. Another child developed macrotrabecular variant in metastasis and died.

In our study we tried to find out the relationship between high β-HCG at presentation and outcome. Two children were presented with high β-HCG level and both of them died. Male child with high β-HCG presented with features of male isosexual precocious puberty. So high β-HCG at presentation is suggestive of poor outcome.

At presentation all children had normal liver function and creatinine value except 3 of them who presented with obstructive jaundice due to central quadrant tumor.

2 children presented with multiple lung metastasis. One child was not operated in view of marginally resectable liver tumor with persistent multiple lung metastasis after 4 courses of PLADO chemotherapy and he died. Other one is well and alive.

Preoperatively on an average the children received 4 cycles of PLADO (cisplatin/doxorubicin combination chemotherapy), ranging from 2 to 6 cycles.

One child had simultaneous presentation of Hepatoblastoma and right paravertebral neuroblastoma and he was treated successfully.

Following neoadjuvant chemotherapy, child with small cell undifferentiated tumor had AFP value of 2.68 IU/ml. In 4 children AFP value came in between 10-100 IU/ml and all of them are alive (survival 100%). The other 23 children had AFP value between 100 IU/ml and 30000 IU/ml). Survival among these 23 children was 43%.

In our series, among 28 patients, PRETEXT and POSTTEXT staging were done on 25 patients. PRETEXT staging distribution was as follows; PRETEXT Stage I 16% (n=4), Stage II 48% (n=12), Stage III 24% (n=6), and Stage IV 12% (n=3). The overall survival according to the PRETEXT stage was as follows: PRETEXT I, 50%; PRETEXT II, 91.66%; PRETEXT III, 16.66%; and PRETEXT IV, 0%.

In our series, Among 28 (N=28) patients, 20 patients underwent hepatic resection (71.42%). Remaining 7 patients did not undergo surgery. Extensive residual disease with metastasis was the major reason behind this. Among 20 patients, 7 had undergone right hemihepatectomy, 3 had undergone right trisectionectomy, 4 were treated with left hemihepatectomy, only 1 child had undergone left lateral sectionectomy and remaining 5 children had undergone segmentectomy. There was no intraoperative and immediate postoperative mortality.

Postoperatively on an average children received 2 cycles of cisplatin and doxorubicin (PLADO).

One patient seems cured with chemotherapy alone. This 3 years girl presented with exomphalos and liver mass was protruding through it. At presentation AFP was 856 IU/ml. The tumor was central in location and PRETEXT stage was III. 6 cycles of PLADO were given. POSTTEXT stage was III. Recent AFP value was 0.596 IU/ml. PET-CT was done, showing no tumor activity.

Disease free survival was 10 months. There might be association of Beckwith-Weidemann syndrome and hepatoblastoma.

Among 28 children, 4 had recurrent disease at remaining liver tissue and 3 had distant metastasis at lung, brain and skull. All 7 patients died.

In our series, 65% patients who underwent hepatic resection are disease free after mean follow-up of approximately 3 years. One patient is disease free after getting full course chemotherapy without surgery. However 7 patients who were originally seen did not undergo surgery for a variety of reasons making the oveall survival 50%.

In most series, the PRETEXT I survival is 100%. But in our series, it is 50%. Among 4 patients of PRETEXT I, 2 patients died. 1 patient had recurrence at remaining left lobe. Other patient had metastases at lung and brain.

CONCLUSION

- Our experience with hepatoblastoma reaffirms the advantages of neoadjuvant chemotherapy, surgery and followed by adjuvant chemotherapy.

- Children whose AFP values come down in between 10-100 IU/ml following neoadjuvant chemotherapy will have good prognosis.

- Most important determining factor in the outcome of children with hepatoblastoma is a combination of complete surgical resection and chemotherapy.

- Children with small cell undifferentiated (SCU, formerly Anaplastic) and macrotrabecular subtype will have poor prognosis.

- Children with high β-HCG at presentation will have dismal outcome.

- Children with unresectable tumor after neoadjuvant chemotherapy and children with recurrent tumor will have poor outcome.

RECOMMENDATIONS

- Neoadjuvant chemotherapy is needed for all stages of hepatoblastoma.

- For surgically unresectable, nonmetastatic disease involving both lobes, orthotopic liver transplantation is an emerging modality of treatment.

- Primary liver transplantation may be associated with better disease-free survival as compared with rescue liver transplantation.

- The potential benefit of transcatheter arterial chemoembolization or hepatic arterial chemoembolization over systemic chemotherapy as initial therapy for unresectable tumors will have to be determined.

ANNEXURE-I

Christian Medical College, Vellore

Department of Paediatric Surgery

Clinical Profile of Children WithHepatoblastoma.

Information sheet

Your child has been invited to join a research study to look at the present status of your child to improve current knowledge of disease – liver tumour (Hepatoblastoma) suffered by him/her. Please take whatever time you need to discuss the study with your family and friends, or anyone else you wish to. The decision to let you child join, or not to join, is up to you.

In this research study, we are evaluating the outcome of Hepatoblastoma. This study will help other children who later come to hospital with the same complaints. By agreeing to be a part of this study, you will contribute to recognizing early how severe the disease is and thereby starting appropriate treatment immediately. The severity of your disease and the final treatment received will be compared to the information collected from you in the beginning.

WHAT IS INVOLVED IN THE STUDY?

This study is follow up study and does not involve any intervention on your child. Your child and you will be asked to give following information

1. History – This includes details regarding your general health and the illness which your child been treated for
2. Clinical examination – Includes evaluation by the attending doctor.

3. Investigations – Includes the results of relevant blood tests, radiological investigations, and biopsy reports. These will be collected from hospital records as well.

We think this will take him/her 30minutes.

Whether you accept or decline to be a part of this study will not affect your further treatment at this hospital.

Your child can stop participating at any time. If your child stops he/she will not lose any benefits.

RISKS

There is no disadvantage or complication that can happen to you by participating in this study as this study does not interfere in the treatment provided by the care taker.

BENEFITS TO TAKING PART IN THE STUDY?

The benefits of joining in this study will be that the treating doctor will gain a better understanding of your child's disease and its process thereby help in improving treatment protocols for the same.

CONFIDENTIALITY

Your child's name will not be used when data from this study are published. Every effort will be made to keep clinical records, research records, and other personal information confidential.

YOUR RIGHTS AS A RESEARCH PARTICIPANT?

Participation in this study is voluntary. Your child has the right not to participate at all or to leave the study at any time. Deciding not to participate or choosing to leave the study will not result in any penalty or loss of benefits to which your child is entitled.

CONTACTS FOR QUESTIONS OR PROBLEMS?

In case of doubts/ questions, please contact Dr. SoumitraSaha, DeptOf Paediatric Surgery, CMCH Vellore. Ph no: +919159595579

Informed Assent form to participate in a clinical trial

Christian Medical College, Vellore

Department of Paediatric Surgery

Clinical Profile of Children With Hepatoblastoma

Study Title:

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access.

However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

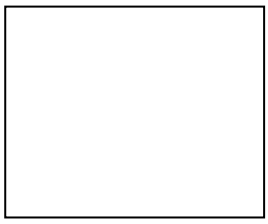
(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

ANNEXURE-II

A Clinical Profile of Children With Hepatoblastoma

PROFORMA

Serial NO. **Hospital No.**

Name: Gender:

Address:

Mobile or Landline No.:

Age of presentation(months):

Mode of presentation:

Mode of diagnosis:

1.Trucut Biopsy

2. Open Biopsy

3. Primary Surgery

4. Raised AFP and Radiological features

Alpha-Fetoprotein (IU/ml):

1. At presentation
2. Before surgery
3. In the last follow-up

Beta-HCG at presentation (mIU/ml)

Liver Fuction Test at presentation:

Creatinine(mg/dl) at presentation:

Histopathology:

1. Special biopsy: (Trucut)
2. Surgical specimen:

PRETEXT (Extent of tumor at diagnosis)

Neoadjuvant chemotherapy: (Cisplatin + Doxorubicin) No of cycles:

POSTTEXT (Extent of tumor after neoadjuvant chemotherapy):

Location of tumor:

Type of hepatectomy:

If not operated. Why?

Recurrences: Yes/ No

Site of recurrence:

Disease free survival:

Death:

1. Early
2. Late

Special features:

ANNEXURE-III

Sr.I	NAME	SEX	HOSPIT	AG	MODE OF I	Mode of di	AFP A	Pulmor	PRETEXT	NEOADJU	POSTTEXT	AFP before	TYPE OF H	ADJUVAN	Recurren	Metastasis	Chemo for r	REDOSUR(	DISEASE F	AFP(I	DEA
1	Haripras	M	497345C	24	Abdominal	Trucut biop	300	No	III V0 P0 E	PLADO:3	III V0 P0 E0	300	Rt. Trisecti	PLADO:1	Lt.lobe	Omentum	(cyclophos	Excision of	Not applica	30000	Yes
2	Rithick.B	F	474650C	16	Abdominal	Trucut biop	300	No	II V0 P0 E0	PLADO:3	II V0 P0 E0	72.5	Segmentect	PLADO:2	No	No		No	75	1.22	No
3	Akkil Ste	M	519625C	54	Abdominal	Trucut biop	300	No	I V0 P+ E0	PLADO:4	I V0 P+ E0	300	Rt.hemihep	PLADO:1	Lt.lobe	Terminal ile	PLADO-1,S	Wide local	Not applica	3E+05	Yes
4	Sourav Ji	M	590170C	8	Abdominal	Trucut biop	300	No	III V0 P0 E	PLADO:7	II V0 P0 E0	300	Rt.hemihep	0	No	No	No	No	86	0.625	No
5	Subham	M	674115C	18	Abdominal	Trucut biop	300	No	I V0 P0 E0	PLADO:5	I V0 P0 E0	9020	Lt. lateral s	PLADO:1		Lung,Brain	No	No	Not applica	7920	Yes
6	Bilal Kha	M	637921C	8	Abdominal	Trucut biop	30000	No	IV V+ P+ E	PLADO:2,J	IV V+ P+ E0	2610(after 5	cycles of JE	0		Multiple bones(skull)			Not applica	>300	Yes
7	Dinesh	M	838990C	12	Abdominal	Trucut biop	30,000	No	II V0 P0 E0	PLADO:4	II V0 P0 E0	594	Segmentect	PLADO:5	No	No	No	No	72	0.401	No
8	Jecynta	F	793007C	13	Abdominal	Trucut biop	30,000	No	****	PLADO:4	II V0 P0 E0	30000	Rt.extended	Ifosfamide+	Etoposid	Lung		No	Not applica	20500	Yes
9	Ratul	M	989981C	24	Abdominal	Trucut biop	300	No	II V0 P0 E0	PLADO:4	II V0 P0 E0	12400	Segmentect	Not given	No	No	No	No	9	1.13	No
10	Akash	M	059700D	11	Abdominal	Trucut biop	30000	No	II V0 P+ E0	PLADO:4	II V0 P+ E0	83.4	Rt.Trisectio	Not given	No	No	No	No	61	0.366	No
11	Amiyo	M	955916C	13	Abdominal	Trucut biop	30000	No	****	PLADO:3,T	****			Not given						>300	Yes
12	Bishruta	M	175206D	30	Abdominal	In view of I	>30000	No	II V0 P0 E0	PLADO:4	II V0 P0 E0	2320	Rt.hemihep	PLADO:5	No	No	No	No	41	1.11	No
13	Deep Dut	M	170946D	24	Abdominal	Trucut biop	>30000	Multip	III V+ P+ E	PLADO:4	III V+ P+ E0	>30000	*	*	*		*	*	*	*	Yes
14	Prithiba	M	349163D	22	Abdominal	Trucut biop	>30000	No	III V0 P+ E	PLADO:5	II V0 P0 E0	>30000	Central qua	PLADO:6	No	No	*	*	Not applica	20700	Yes

15	Nithin	M	447111D	10	Abdominal	Trucut biop	4.32	No	II V0 P0 E0	PLADO:4	II V0 P+ E0	2.68	Left hemihe	PLADO:5, [	Liver metastasis(USG		No	No	Not applica	*	Yes
16	Malsaw	F	501643D	24	Abdominal	Trucut biop	2310	No	I V0 P0 E0	PLADO:4	I V0 P0 E0	8540	Segmentect	PLADO:5,6	No	No	No	No	5	3.25	No
17	Jagan. T	M	531534D	12	Abdominal	Laparotomy	>30000	No	II V0 P0 E+	PLADO:6	II V0 P0 E+	C0 M0	Rt.hemihep	No post op	No	No	No	No	19	1.13	No
18	Amir Sul	M	535881d	24	Abdominal	Trucut biop	>30000	No	III E0 C0 M	Carboplatin	II V0 P+ E+	4300	Left hemihe	5th course	Recurren	No	Palliative ch	Resection o	Not applica	75000	Yes
19	Soura Da	M	556291D	12	Abdominal	Trucut biop	>30000	No	I V0 P+ E0	PLADO:1,2	I V0 P+ E0	20.7	Left hemihe	PLADO:5	No	No	No	No	27	1	No
20	Mohmed	M	633318D	9	Abdominal	Trucut biop	5E+05	No	IV V0 P+ E	PLADO:1,2	III V0 P+ E0	1180(PLAD	*	*	*		*	*	*	2E+05	Yes
21	JOSEPH S	M	741300D	32	Abdominal	Trucut biop	4E+06	Multip	II V0 P+ E0	PLADO X 5	II V0 P0 E0	2390	Rt.hemihep	Carboplatin	No	No	No	No	26	0.731	No
22	Jonita	F	848823D	15	Abdominal	In view of C	2E+05	No	II V+ P0 E0	PLADO X 4	II V+ P0 E0	1980	Rt.hemihep	PLADO:5,6	No	No	No	No	22	0.836	No
23	BHAVADI	F	094944F	36	Abdominal	Trucut biop	856	No	II V0 P+ E+	Cisplatinx1	II V0 P+ E+	*	*	*	No	No	NA	NA	10	0.596	No
24	Aleena R	F	195955F	7	Abdominal	In view of C	>30000	No	II V0 P+ E0	Cisplatinx1	I V0 P0 E0	C 30.2	Rt.hemihep	PLADO:5	No	No	No	No	7	6.52	No
25	Akash Pa	M	208039F	10	Abdominal	Trucut biop	>30000	No	IV V0 P+ E	Cisplatin X	IV V0 P0 E0	*	*	*	*		*	*	*	59400	Yes
26	Ranjeeth	M	216105F	##	Abdominal	Trucut biop	3E+05	No	II V0 P0 E0	Cisplatin X	I V0 P0 E0	C 2020	Left hemihe	PLADO:5,6	No		No	No	6	1.4	No
27	Tshering	M	238302F	24	Abdominal	Trucut biop	2E+05	No	****	Cisplatin X	II V0 P0 E0	C0 M0	*	*	No	No	*	*	*	*	Yes
28	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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